IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Thomason *et al.*

Serial No.: 09/391,861 Group Art Unit No.: 1632

Filed: September 7, 1999 Examiner: S. Preibe

For: FIBROBLAST GROWTH FACTOR-LIKE POLYPEPTIDES

Docket No.: 99-371

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. DAVID ORNITZ UNDER 37 C.F.R. § 1.132

Sir:

1. I hold a B.S. in Biochemistry from the University of California, Davis, which I received in 1981, a Ph.D. in Biochemistry from the University of Washington, Seattle, which I received in 1987 and an M.D. from the University of Washington, Seattle, which I received in 1988. From 1988-1992 I performed postdoctoral research at the Harvard University Medical School, where my research focused, in part, on Fibroblast Growth Factors, more specifically I discovered FGF receptor 3 based on similarity to FGF receptor 1. I also demonstrated that FGF3 could cause mammary gland cancer in transgenic mice. I currently hold the position of Alumni Endowed Professor of Molecular Biology and Pharmacology at Washington University, St. Louis, Missouri. I am also the Interim Chair of the Department of Molecular Biology and Pharmacology at Washington University.

2. I am not now, nor have I ever been, an employee of Amgen Inc. Prior to my work on this declaration, for which I was paid my normal hourly consulting fee, I have never personally received any financial compensation from Amgen Inc.

3. I am the author or coauthor of over 125 scientific publications, approximately 100 of which are peer-reviewed research articles or review articles. Approximately 75% or more of these publications are related to Fibroblast Growth Factors. A copy of my current *curriculum vitae* is attached hereto as Exhibit A.

4. A primary focus of my current research is Fibroblast Growth Factors ("FGFs") and Fibroblast Growth Factor Receptors ("FGFRs"). I have been active in this field of research since approximately 1988. Accordingly, I am familiar with FGF structure, sequence and function, as well as the techniques and knowledge available to researchers in the field of FGFs at the time U.S. Patent Application No. 09/391,861 ("the Patent Application") was filed, having been active in that field of research at that time myself. In addition, my past training in medicine has given me perspective on diagnostic and therapeutic uses of molecules identified through molecular biological and genetic studies.

5. It was clear to me that the new FGF described in the Patent Application is a new member of the FGF family, which was unpublished before the Patent Application was filed, in view of the fact that (a) the sequence of the new FGF is more like other FGFs than any other molecule, and (b) the conserved FGF core domain, which is found in all FGFs, is present in the new FGF.

I reviewed the sequence of the new FGF presented in Figure 3A-3D and recognized specific residues known prior to the date the Patent Application was filed to be conserved in all FGFs. These residues in Figures 3A-3D of the Patent Application, including for example residues 99, 100, 140, 161, 176, 183 and 186 are found in most FGFs and were known to define the FGF family. This information was subsequently published by Plotnikov et al., (Exhibit B, Plotnikov et al., (2000) Cell 101:413-24; published in May 2000, based on the information known in the art before the Patent Application was filed). Thus, I conclude the new FGF is in fact a member of the FGF family.

6. Based on (a) the high degree of sequence identity between the mouse and human nucleic acid and polypeptide sequences of the new FGF described in the Patent Application, and (b) the data showing that both genes are expressed exclusively in the liver, it was clear to me that the human nucleic acid and polypeptide sequences of the new FGF described in the Patent Application are orthologs of the mouse sequences.

7. It was clear to me that the experiments involving transgenic animals overexpressing the new FGF described in the Patent Application were actually performed because the results presented in the Patent Application identify a phenotype that appears to result from transgenic overexpression of the new FGF described in the Patent Application in multiple lines of mice (i.e., using ApoE or beta actin gene regulatory elements).

8. At the time the Patent Application was filed, a number of known FGFs, such as FGF2 (Exhibit C, Hull et al., (1997) Gut 40(2):204-210) and FGF7 (Exhibit D, Hsu et al., (1999) Biochem. 38:2523-34), were being evaluated for therapeutic uses. It is reasonable, therefore, to believe that the new FGF described in the Patent Application could also be used therapeutically. Based on my review of the Patent Application, I expect that at the time the Patent Application was filed, the new FGF described in the Patent Application could be used as a regulator of metabolic activity and could be used as a therapeutic molecule in the treatment of a variety of metabolic diseases. Examples of specific conditions that could be treated include diabetes and obesity. I base my conclusion on several factors.

First, the transgenic animals have a systemic phenotype, indicating that the new FGF has distal effects.

Second, the new FGF is expressed in liver, has an identified signal peptide and thus would be typically secreted into the bloodstream or into the intestine and therefore is likely to act on tissues outside the liver. This was a novel concept at the time the application was filed but is fully supported by the data in the Patent Application, particularly the phenotype of the transgenic mice.

Third, as an FGF, the new FGF is expected to have the properties of other FGFs, such as the ability to activate receptors and have FGF-like effects, including affecting cell regulation, differentiation and physiology.

Fourth, of the many activities FGFs are likely to have, the new FGF appears to have unique activities as pointed out in the Patent Application. The new FGF was shown to act at a significant distance from its site of expression, for example regulating body weight and possibly fat deposition.

Fifth, based on its unique expression in liver, it is possible that the new FGF directly regulates liver function and through this mechanism regulates metabolic activity. It was known at the time the Patent Application was filed that FGF molecules form subfamilies and differentially activate the seven major FGFRs (1b, 1c, 2b, 2c, 3b, 3c and 4). It was also known that FGFs require cofactor molecules to regulate their interaction with FGFRs. Thus,

as described in the Patent Application on page 67, lines 10-11, specific cofactors may determine whether the new FGF acts directly on the liver or on distal target tissues.

9. Based on my review of the Patent Application, I believe that at the time the Patent Application was filed the new FGF described in the Patent Application could be considered for use as a diagnostic molecule for assessing liver function. This conclusion is based on data shown from both mouse and human that the new FGF is made exclusively in liver, that it has a signal peptide and is therefore likely secreted and its sequence is unique enough such that monoclonal or polyclonal antibodies can easily be made to detect the presence of the new FGF in the bloodstream, bile or other bodily fluids.

10. As a result of my research on FGF signaling, I have identified functions of FGFs that are both stimulatory and inhibitory for different cellular processes. For example, activating FGFR3 can inhibit the growth of chondrocytes but can activate the growth of other cell types. Therefore, based on the phenotype of the transgenic mice that express this new FGF, it is not surprising to me that one property of this new FGF is to inhibit growth or metabolic activity and thus cause weight loss.

11. All of the statements I made herein are truthful and made of my own volition. I understand that willful false statements may subject me to fines, imprisonment or both, pursuant to Section 1001 of Title 18 of the United States Code.

Dr. David Ornitz